THE BULLETIN OF
Mathematical BIOPHYSICS

THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 5
NUMBER 2
JUNE 1943

THE BULLETIN OF
Mathematical Biophysics
EDITED BY N. RASHEVSKY

The Bulletin is devoted to publications of research in Mathematical Biophysics, as described on the inside back cover.

THE BULLETIN is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $2.50 per year, the price of single copies is 75 cents. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to The University of Chicago Press in postal or express money orders or bank drafts.

THE FOLLOWING are authorized agents:

For the British Empire, except North America, India, and Australasia: The Cambridge University Press, Bentley House, 200 Euston Road, London, N.W. 1. Prices of yearly subscriptions and of single copies may be had on application.

CLAIMS FOR MISSING NUMBERS should be made within the month following the regular month of publication. The publishers expect to supply missing numbers free only when losses have been sustained in transit, and when the reserve stock will permit.

BUSINESS CORRESPONDENCE should be addressed to The University of Chicago Press, Chicago, Ill.

COMMUNICATIONS FOR THE EDITOR and manuscripts should be addressed to N. RASHEVSKY, Editorial Office of the Bulletin of Mathematical Biophysics, 5822 Drexel Avenue, Chicago, Ill.

PRINTED BY THE DENTAN PRINTING CO., COLORADO SPRINGS, COLORADO

BULLETIN OF
Mathematical Biophysics

CONTENTS

VOLUME FIVE JUNE 1943 NUMBER TWO

IMPORTANT ANNOUNCEMENT

The increase in the output of papers in the field of mathematical biophysics makes it difficult to insure prompt publication without an increase in the size of the journal. Therefore, the Bulletin of Mathematical Biophysics inaugurates the following service:

Upon acceptance of a paper, the Editor, if necessary, will ask the author to shorten the paper to an extent dictated by the requirements of a reasonably prompt publication. The shortening should in no case reduce the paper to a mere abstract. Such a shortened paper will be published within six months or less.

The unabbreviated original manuscript will be kept on file at the editorial office. Any person desiring to avail himself of the complete manuscript, may obtain promptly a microfilm copy of the latter, at the cost of 1¢ per page plus postage, by applying to the Editorial Office, 5822 Drexel Avenue, Chicago, Illinois.

All papers in the Bulletin which have been thus shortened, will be marked at the end by the symbol MF, followed by a figure, indicating the number of doublespaced typewritten pages of the unabbreviated manuscript.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 5, 1943

OUTLINE OF A NEW MATHEMATICAL APPROACH TO GENERAL BIOLOGY: II

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

In this continuation of a previous paper another formal principle is added, similar in its form to Hamilton's principle in mechanics, and based on a mathematical formulation of a postulate, stated by A. J. Lotka, namely that the events in the living world are determined by the requirement of the maximum of the total *flow of energy*.

The principle is applied to a wide number of biological phenomena, including paleontologic developments, relations between death and birth rates of organisms, ontology, cell division, etc.

II. The Organic World as a Whole

The environment of each organism being principally composed of other organisms, the organic world as a whole is characterized by an incessant interaction between different organisms. Some of them provide food for the others. Some are detrimental to others either by feeding on them or inhibiting the activities of these others by metabolic by-products (bacterial toxins). Thus the whole organic world is a system in which continuous exchanges of matter and energy takes place, a system of complex flows of matter and energy.

A. J. Lotka (1922a, b) suggested as a possible general biological principle, that the processes of life run in such a way as to maximize the total flow of energy in the organic world. We shall attempt to develop this suggestion further, and formulate it in mathematical form. We shall first proceed in a purely abstract fashion.

Let any organism be completely determined by n determining parameters

$$x_1 , x_2 , x_3 \cdots x_n . \tag{1}$$

Consider first the case that those parameters have only a finite set of discrete values

$$\begin{aligned} &x_1^{(1)} , x_2^{(1)} , x_3^{(1)} \cdots x_n^{(1)} \\ &x_1^{(2)} , x_2^{(2)} , x_3^{(2)} \cdots x_n^{(2)} \\ &\cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \\ &x_1^{(m)} , x_2^{(m)} , x_3^{(m)} \cdots x_n^{(m)} \end{aligned} \tag{2}$$

where in general $m > n$, and m is in no way related to n. Subsequent-

ly we shall pass to the continuous case, letting all x_i's vary continuously.

Consider an organism, that is characterized by the following set of determining parameters.

$$x_1^{k_1}, x_2^{k_2}, x_3^{k_3} \cdots x_n^{k_n} \tag{3}$$

and let the total number of such organisms in the organic world be

$$N_{k_1,k_2 \ldots k_n}. \tag{4}$$

Let another organism be characterized by a set of values

$$x_1^{l_1}, x_2^{l_2}, x_3^{l_3} \cdots x_n^{l_n}, \tag{5}$$

and the total number of organisms of that type be

$$N_{l_1,l_2 \ldots l_n}. \tag{6}$$

We may denote the energy exchange of interaction of the first kind of organisms with the second kind by

$$a_{k_1,k_2 \ldots k_n; l_1,l_2 \ldots l_n} N_{k_1 \ldots k_n} N_{l_1 \ldots l_n}. \tag{7}$$

The coefficient $a_{k_1 \ldots k_n; l_1 \ldots l_n}$ is to be considered as positive if the interaction is such, that it increases the energy content of the first type of organisms, negative—otherwise.

The total energy of interaction or total exchange in the whole organic world is then given by the sum

$$I_0 = \sum_{k_i} \cdots \sum_{l_i} a_{k_1 \ldots k_n; l_1 \ldots l_n} N_{k_1 \ldots k_n} N_{l_1 \ldots l_n}. \tag{8}$$

We may also consider the interaction of each type of organism with the inorganic world; this will be of the form

$$I_i = \sum_{k_i} b_{k_1 \ldots k_n} N_{k_1 \ldots k_n}. \tag{9}$$

It may be remarked, that we do not need necessarily to have $a_{ik} = -a_{ki}$, as one might be inclined to assume at first. The antisymmetry would be required only if the organisms would interact in isolated pairs. In general, when there is simultaneous exchange of energy between many organisms, $a_{ik} \gtrless -a_{ki}$.

We may now consider different types of postulates that lead us to interesting equations, governing the development and behavior of the organic world.

First we may postulate that the configuration of the whole organic world tends to such a configuration which maximizes the value

$I_0 + I_i$. When such a configuration is reached, no further changes occur, and if $F(N_{k_1 \ldots k_n})$ is any function of $N_{k_1 \ldots k_n}$

$$\frac{dF(N_{k_1 \ldots k_n})}{dt} = F'(N_{k_1 \ldots k_n}) \frac{dN_{k_1 \ldots k_n}}{dt} = 0, \tag{10}$$

where F' denotes the derivative.

At the same time, when $I_0 + I_i$ has a maximum

$$\frac{\partial (I_0 + I_i)}{\partial N_{k_1 \ldots k_n}} = 0. \tag{11}$$

Hence, it is natural to put

$$\frac{dF(N_{k_1 \ldots k_n})}{dt} = \frac{\partial (I_0 + I_i)}{\partial N_{k_1 \ldots k_n}}, \tag{12}$$

where F is to be determined later by biological considerations. Introducing equations (8) and (9) into (12) we find

$$\frac{dF(N_{k_1 \ldots k_n})}{dt} = \sum_{l_i} a_{k_1 \ldots k_n; l_1 \ldots l_n} N_{l_1 \ldots l_n} + b_{k_1 \ldots k_n}. \tag{13}$$

If we now let the values of $x_i^{(m)}$ vary continuously, the coefficients $a_{k_1 \ldots k_n; l_1 \ldots l_n}$ become functions of the values $x_1, x_2 \cdots x_n$ of the first organism and of the values $x_1', x_2' \cdots x_n'$ of the second. The coefficient $b_{k_1 \ldots k_n}$ become functions of $x_1, x_2 \cdots x_n$, $N_{k_1 \ldots k_n}$ becomes a function $N(x_1 \cdots x_n)$ of $x_1, x_2 \cdots x_n$, $N_{l_1 \ldots l_n}$ becomes a function $N(x_1' \cdots x_n')$ of the x_i''s and the system of linear differential equations (13) becomes an integrodifferential equation of the form

$$\begin{aligned} &F'\{N(x_1, \cdots x_n, t)\} \frac{\partial N(x_1, \cdots x_n, t)}{\partial t} \\ &= \int\int \cdots \int K(x_1, \cdots x_n; x_1' \cdots x_n')\, N(x_1' \cdots x_n')\, dx_1' \cdots dx_n' \\ &+ f(x_1, x_2 \cdots x_n), \end{aligned} \tag{14}$$

the integration being extended over the whole range of variation of the x_i''s.

If the kernel $K(x_1, x_2 \cdots x_n; x_1' \cdots x_n')$ and the function $f(x_1, x_2 \cdots x_n)$ are known, the integrodifferential equation (14) determines for given initial conditions, $N(x_1; \cdots x_n, t) = N_0(x_1, \cdots x_n)$ for $t = 0$, the function $N(x_1, \cdots x_n, t)$ for any time $t > 0$. Since the values of $x_1, x_2 \cdots x_n$ determine the shapes and sizes, and in general

the anatomic structure of the organism, the knowledge of $N(x_1, x_2 \cdots x_n, t)$ gives us thus the distribution of different types of organisms in the organic world at any time $t > 0$. For certain values of the x_i"s the function $N(x_1, \cdots x_n, t)$ may be zero. Organisms with anatomic structure corresponding to such values of the determining parameters will not exist. As we have remarked elsewhere (Rashevsky, 1941), the knowledge of the distribution function $N(x_1, \cdots x_n, t)$ gives us also the correlation coefficient between the different determining parameters, if $n = 2$. For practical purposes, whatever we may wish to obtain from equation (14), it will be rather difficult to do for such a large number of determining parameters as is likely to actually occur. We may however fix our attention on any pair x_r, x_s of the n determining parameters, and wish to find the correlation between them, when the remaining $n - 2$ determining parameters vary at random. To this end we may integrate the function $N(x_1, x_2 \cdots x_n)$ with respect to all the variables except x_2 and x_3, the integration to be extended over the whole range of variation of those $n-2$ variables. Thus we obtain

$$\bar{N}(x_r, x_s, t) = \int \cdots \int N(x_1, \cdots, x_n, t)\, dx_1 dx_2 \cdots dx_{r-1}\, dx_{r+1} \cdots dx_{s-1}\, dx_{s+1} \cdots dx_n . \tag{15}$$

Since, denoting by $N(t)$ the total number of organisms in the world at the time t, we have

$$\int \cdots \int N(x_1, \cdots x_n)\, dx_1 \cdots dx_n = N(t) , \tag{16}$$

therefore

$$\int \int \bar{N}(x_r, x_s, t)\, dx_r\, dx_s = N(t). \tag{17}$$

Hence $\bar{N}(x_r, x_s, t)$ may be considered as a distribution function for x_r and x_s for random values of the other determining parameters.

By introducing similarly a function

$$\bar{K}(x_r, x_s; x_r', x_s') = \int \cdots \int K(x_1 \cdots x_n; x_1' \cdots x_n')\, dx_1 \cdots dx_{r-1}\, dx_{r+1} \cdots dx_{s-1}\, dx_{s+1} \cdots dx_n \cdots dx_1' \cdots dx'_{r-1}\, dx'_{r+1} \cdots dx'_{s-1}\, dx'_{s+1} \cdots dx'_n$$

and by applying the same reasoning to $\bar{N}(x_r, x_s)$ in regard to mutual interaction, we find

$$F'\{N(x_r, x_s, t)\} \frac{\partial \bar{N}(x_r, x_s, t)}{\partial t} = \int \int \bar{K}(x_r, x_s) \bar{N}(x_r', x_s')\, dx_r'\, dx_s' + \bar{f}(x_r, x_s) , \tag{18}$$

where

$$\bar{f}(x_r, x_s) = \int \cdots \int f(x_1 \cdots x_n)\, dx_1 \cdots$$

$$dx_{r-1}\, dx_{r+1} \cdots dx_{s-1}\, dx_{s+1} \cdots dx_n .$$

Equation (18) may be used for the determination of the coefficient of correlation between x_r and x_s and to the extent that those may determine certain features of the anatomic structure, it may be used for a theoretical prediction of the correlation between some anatomic structures.

Equation (14) describes the gradual development of the whole organic world. The change of $N(x_1, \cdots x_n, t)$ in time gives us the change of the general structure of the organic world with changes from one type of organism to another, as is found in paleontology. One of the problems of the theory is to determine $K(x_1 \cdots x_n; x_1' \cdots x'_n)$ and $f(x_1 \cdots x_n)$ from theoretical considerations, and to see whether this will give us such an $N(x_1 \cdots x_n, t)$ which would roughly describe paleontological facts.

If $f(x_1 \cdots x_n) > 0$ for any values of $x_1 \cdots x_n$, equation (14) implies that even when $N(x_1 \cdots x_n) = 0$, still for every set of values of $x_1 \cdots x_n$, $\partial N(x_1 \cdots x_n)/\partial t > 0$. This would mean, that organisms of any type could be spontaneously generated from nonliving material. Since this is not the case $f(x_1, \cdots x_n)$ cannot be positive everywhere. Neither can it be negative or zero everywhere, since then the organic world could never have started, because if $f(x_1 \cdots x_n) \leqq 0$, then for $N(x_1, \cdots x_n) = 0$, $\partial N(x_1 \cdots x_n)/\partial t \leqq 0$. At some geological epoch life must have started out of the nonliving. And it did start with the simplest organisms for which most of the x_i's are zero, and the others, perhaps only M and q, rather small. To obtain this result we may assume $f(x_1 \cdots x_n)$ to be of the following form.

Let

$x_1 = M$, $x_2 = q$, and let Δ, ε_1 and ε_2 be small positive quantities. Then let

$$f(x_1, x_2 \cdots x_n) = \Delta \text{ for } 0 < x_1 < \varepsilon_1,\ 0 < x_2 < \varepsilon_2,\ x_3 = x_4 = \cdots = x_n = 0$$

$$f(x_1, x_2 \cdots x_n) = 0 \text{ for any } x_i > 0, \quad i > 2 . \tag{19}$$

With such a form of f, we shall find that even when $N(x_1 \cdots x_n) = 0$, $\partial N(x_1 \cdots x_n)/\partial t > 0$ for such organisms, which correspond to $0 < x_1 < \varepsilon_1$; $0 < x_2 < \varepsilon_2$. But $\partial N(x_1 \cdots x_n)/\partial t = 0$ for all higher organisms, which have any of the x_i $(i > 2)$ greater than zero.

Such a situation would still imply, that even at the present time the spontaneous generation of some lowest forms of organisms takes

place. Though there is no direct evidence against that, if such an evidence were forthcoming, it could be met in two different ways.

A. The first and simplest way is to make f depend on one or more parameters $\eta(t)$ which vary with time. Those parameters may characterize the physico-chemical properties of the environment, such as temperature, pressure, humidity, etc. at different times. We may now put instead of (19), a different requirement, namely:

Requirement (19) holds only for $\eta < \eta_0$; for $\eta > \eta_0$ $f(x_1, x_2 \cdots x_n) = 0$ for any values of x_i. If now η increases with time, being originally less than η_0, then after a while spontaneous generation will become impossible, for any kind of organisms, no matter how simple.

B. The second way is to make f not a function of the x_i's, but a functional of $N(x_1 \cdots x_n)$; in Volterra's notations $f|[N(x_1 \cdots x_n)]|$, such that

$$f|[N(x_1 \cdots x_n)]| > 0$$

when $N(x_1 \cdots x_n)$ is different from zero only for $0 < x_1 < \varepsilon_1$; $0 < x_2 < \varepsilon_2$, $x_3 = x_4 \cdots = x_n = 0$ and

$$f|[N(x_1, \cdots x_n)]| = 0$$

for any other shapes of $N(x_1, \cdots x_n)$. In that case, f will become zero as soon as the organic world develops sufficiently to have even a few organisms with $x_i > 0$ $(i > 2)$.

There is, however, a good reason why the proposed equation should in principle not be adequate to take care of the problem of the origin of life. This reason we shall discuss in a subsequent paper. For the time being we shall keep the f term, since an exchange of energy with environment always takes place, and take care of the general non-occurrence of spontaneous generation at the present time by a proper choice of the function F.

The equation

$$K(x_1, \cdots x_n;\ x_1' \cdots x_n') = 0 \tag{20}$$

defines for a given set of values $x_1 \cdots x_n$, considering x_i's as variables, an n — dimensional hypersurface, which divides the whole space of the variables x_i' in two regions, one for which $K > 0$, and another for which $K < 0$. The hypersurface (20) may be multiply connected. Let us denote by V_+ the region in the hyperspace for which $K > 0$, and by V_- the region for which $K < 0$. Since $N(x_1 \cdots x_n, t) \geqq 0$, therefore we may write equation (14), thus, denoting by vertical lines absolute values.

$$F'\{N(x_1, \cdots x_n)\} \frac{\partial N(x_1 \cdots x_n, t)}{\partial t}$$
$$= \int_{V_+} \cdots \int |K(x_1 \cdots x_n; x_1' \cdots x_n')| N(x_1' \cdots x_n') \, dx_1' \cdots dx_n' - \int_{V_-} \cdots \int |K(x_1 \cdots x_n; x_1' \cdots x_n')| N(x_1' \cdots x_n') \, dx_1' \cdots dx_n' + f . \tag{21}$$

both integrals being positive.

Considering x_1, $x_2 \cdots x_n$ as fixed, we may interpret the first integral of (21) as the increase of organisms of type $(x_1, x_2 \cdots x_n)$ by birth, while the second integral may be interpreted as the decrease of the number due to death. Both birth and death rates thus appear as depending on the presence of other organisms. For such values of the x_i's, for which $f > 0$, the function f adds to the birth rate, while for such values for which $f < 0$ it adds to the death rate. To bring equation (21) into the usual form, when the birth and death rates are proportional to the population, we must put

$$F\{N(x_1 \cdots x_n)\} = \log N(x_1 \cdots x_n). \tag{22}$$

Equation (21) then becomes

$$\frac{\partial N(x_1 \cdots x_n, t)}{\partial t}$$
$$= N(x_1 \cdots x_n, t) \int_{V_+} \cdots \int |K(x_1 \cdots x_n; x_1' \cdots x_n')| N(x_1' \cdots x_n') \, dx_1' \cdots dx_n'$$
$$- N(x_1 \cdots x_n, t) \int_{V_-} \cdots \int |K(x_1 \cdots x_n; x_1' \cdots x_n')| N(x_1' \cdots x_n') \, dx_1' \, dx_n' + N f . \tag{23}$$

This may be considered as a more general form of the usual growth equation:

$$\frac{dn}{dt} = an - bn^2$$

which may be written in the form

$$\frac{dn}{dt} = a'n - (b' + c'n)n$$

with

$$a = a' - b' ; \quad b = c' .$$

Thus if the kernel K is known, by means of equation (20) we may

determine the birth and death rates for any species characterized by a given set of values $x_1 \cdots x_n$ of the determining parameters. The knowledge of those quantities gives us also the average lifespan of the species. If the death rate is equal to $q(t)$ and n denotes the total number of individuals at a given time, then, in the absence of birth

$$\frac{dn}{dt} = -q(t)n \tag{24}$$

or

$$n = n_0 e^{-\int q(t)\,dt} \tag{25}$$

which shows that n tends to zero exponentially.

Let the distribution of life-spans of a group or organisms be such, that the number of individuals that die at the age t, is given by

$$n_0 \mathcal{N}(t)\,dt$$

with

$$\int_0^\infty \mathcal{N}(t)\,dt = 1\,. \tag{26}$$

We have for the average $\bar{t}$

$$\bar{t} = \int_0^\infty t\,\mathcal{N}(t)\,dt\,. \tag{27}$$

If we consider that originally all individuals have the same average age, then in absence of births, the number of individuals, originally n_0, becomes at the time t:

$$n_0 - n_0 \int_t^\infty \mathcal{N}(t)\,dt = n_0 \int_0^t \mathcal{N}(t)\,dt\,. \tag{28}$$

Let at the time t^*, this number drop to $1/e$ of its original value. Then we have

$$\int_0^{t^*} \mathcal{N}(t)\,dt = \frac{1}{e} \tag{29}$$

which solved for t^* gives, because of (27)

$$t^* = u(\bar{t}), \text{ or } \bar{t} = \bar{u}(t^*). \tag{30}$$

From (25) we have for the time when n_0 drops to $1/e$ of its original value

$$\int_0^{t^*} q(t)\,dt = 1 \tag{31}$$

which determines t^* for a known $q(t)$. Substituting that value of t^* into the second equation (30), we find $\bar{t}$.

If the distribution of the life spans is due to chance, $\mathcal{N}(t)$ will be the normal distribution and $\bar{t}$ may be found explicitly in terms of the parameters of that normal distribution.

Thus, knowledge of K in equation (23) gives us the birth and death rates and the average life span for any organism.

It may appear strange that both birth and death rates are dependent on the presence of other organisms. Concerning the birth rate this is however quite natural. For the multiplication of organisms goes on only under proper conditions of nutrition, which involve the destruction of other organisms. Even as regards some simplest microorganisms, which feed on non-living media, they do not multiply in a culture where only a few organisms are present.

In regard to death rate the conclusion is no less natural. Equation (23) gives the actual death rate, which is due to all possible causes. And with rare exceptions, death occurs due to interaction with organisms. Death of pure old age is exceedingly rare, even amongst humans. If $f > 0$, then in terms of our equations (23) we may express that death rate by taking the integral

$$\int \cdots \int K(x_1 \cdots x_n; x_1' \cdots x_n')\, dx_1' \cdots dx_n' \tag{32}$$

over a very narrow strip of values in the immediate neighborhood of the hypersurface (20). If η_1 is a small quantity, we may integrate over the range

$$x_i^0 - \eta_1 , x_i^0 + \eta_1 , \tag{33}$$

x_i^0 being a coordinate of a point of the hypersurface (20), and η_1 being considered as the range of biological variations of the characteristics of the species. Expression (32) integrated over the range (33) may be divided again into a positive and negative part, the latter giving us the death rate from purely old age. Due to the smallness of η_1, it will be very small.

The problem of handling equation (23) resolves itself into two parts: first the problem of determining from physico-chemical and biological considerations the form of $K(x_1 , \cdots x_n; x_1' \cdots x_n')$; and second—the solution of the nonlinear integrodifferential equation (23). The similarity of equation (23) to some nonlinear systems of differential equations with many variables studied by V. Volterra (1931) suggests the approach to the second problem by a transition to the continuous case from Volterra's equations. The first problem opens a very wide field for further theoretical studies.

It is important to remark, that the limits of integration in equa-

tions (14) and (23) are not all constant. As we have seen in part I, if M and q are prescribed, the velocity v may have in general an upper limit, which will be a function of M and q. Thus if we deal for instance with only three determining parameters $x_1 = M$, $x_2 = q$ and $x_3 = v$, we may integrate with respect to x_1 and x_2 from 0 to ∞, but with respect to x_3 only from 0 to a value $v(M,q)$. In other words the total space is limited by the planes $q = 0$, $M = 0$, $v = 0$ and the surface $v = v(M, q)$.

Limiting ourselves, for simplicity, to only two determining parameters, M and n, we may for instance determine the form of K by such considerations. For any small value of n the interaction between the two organisms M and M' will be such that the greater the ratio M/M', the greater the interaction. (Remembering that by definition the interaction of M and M' is positive, when it favors M.) This will hold however only within a certain range of ratios M/M'. A too large ratio M/M' may be unfavorable to the first organism.

Thus while an elephant may readily have the better part of a tiger, yet it may be quite helpless against some pathogenic bacteria with which its interaction will be negative. Hence K must for a fixed n vary in such a way as to have a positive maximum for a certain M/M', then drop again and become negative.

But as n increases, the advantage of a larger mass becomes less and less important. A smaller animal with greater nervous coordination may have the better of a larger one with a less developed nervous system. Denoting by A, B, C and D four constants, we may try the following expression for $K(M, n; M', n')$:

$$K(M, n; M', n') = \frac{\frac{M}{M'}\left(A + Bn - \frac{M}{M'}\right) - (A + Bn - 1)}{C + n} + \frac{D + n}{D + n'}. \tag{34}$$

Expression (34) has the property, that for fixed M and n and for very small values of n, the first term is the most important. With increasing n, not only does the first term decrease relatively to the second, but the optimal value of M/M' shifts towards larger values of M/M'. For very large n, the second term becomes the only important one.

Without solving equation (23), we may surmise what consequences of such a choice of K will have. Given an initial condition, when only small values of M and n are present, we shall find that the

larger the value of M, the larger the birth rate and the smaller the death rate. Hence $\partial N(M, n, t)/\partial t$ will be the largest for large values of M, and the value of $N(M, n)$ will become large for large M's. As however the value of $N(M, n)$ increases for all values, and therefore the number $N(M, n)$ of organisms with large n also increases, the birth rate will become largest for organisms with a large n. Such organisms begin to prevail and those with large M, but small n actually die out. (C.f. preponderance of large reptiles in Jurassic era and their recession.)

As a final generalization of our approach we may suggest, that instead of postulating the maximizing of the expression $I_0 + I_1$, as given by expression (8) and (9), we may introduce a Hamiltonian principle and postulate that (Whittaker, 1927, p. 249)

$$\int_{t_1}^{t} (\delta F + \Sigma Q_{k_1 \ldots k_n} \delta N_{k_1 \ldots k_n}) = 0. \tag{35}$$

With

$$F = I_0 + I_i; \quad Q_{k_1 \ldots k_n} = -\frac{1}{N_{k_1 \ldots k_n}} \frac{dN_{k_1 \ldots k_n}}{dt}, \tag{36}$$

requirement (35) leads us to a system of non linear equations, which, in passing to the continuous case lead again to equation (23).

III. Further Applications; General Discussion

Equation (23) or the more general equation (14), represents a theory of the development of the whole organic world. Known facts of paleontology should be deducible from those equations in principle, provided we can overcome the mathematical difficulties of solving them.

We may apply the same principle, which leads to equation (14) or (23) to a number of more restricted, though no less important problems, by generalizing it somewhat. We may assume that the principle (35), or the requirement of the maximum of $I + I_0$, holds not only for the organic world as a whole, but for any part of it. We may apply it then either to limited organic groups, or even to individual organisms or cells.

An example of such a limited group is given by human society. While the gross physiological properties of man may be considered as rather uniform constants, different psychological traits vary considerably from person to person. The social interactions of two individuals are determined by the values of the parameters which measure those psychological traits. By exactly the same argument as in

section *II* we shall arrive at an integrodifferential equation of the form (23) for the determination of the distribution function of different traits. Not only does this equation give the distribution function, but it also gives its variation with time. As has been shown elsewhere (Rashevsky, 1942) such a distribution function determines the social structure of society, and its variation with time. Thus mathematical sociology actually becomes a branch of mathematical biology, and history may in a sense be considered as a small branch of paleontology.

The distribution of different psychological types may also be studied in this way. The methods of theoretically predicting the correlation between any pair of determining parameters, mentioned in section *II*, suggests a possible approach to a theory of the experimentally found correlations between Thurstone's primary factors.

The same procedure should lead to a theory of distribution of different pathological variations, giving us the incidence of certain organic diseases.

All human activities may be considered as biological manifestations and the principle of maximum energy flow may be applied to all of them. If so, then even such problems as the distribution of wealth may be treated in a similar way. Wealth is an important factor producing energy flow, and the Pareto distribution may perhaps be derived from considerations of maximizing that flow.

A characteristic feature of equation (14) or (23) is that they imply the necessity of death in general for all organisms, if the organic world is to function as a whole with a maximum flow of energy. This "necessity of death" may be considered also from another angle, in reference to humans alone. Destruction of one's own fellow men is a process that involves itself a large expenditure of energy and hence produces an energy flow. It may be, that actually the energy flows involved in such a destruction or war, are greater per unit time than those involved in peace time activities. A war however cannot last indefinitely, because it would lead to the extinction of the race. But a maximum energy exchange per unit time may be obtained by intermittent alterations of war and peace.

For simplicity let those alterations be assumed quite regular. Let the duration of peace be t_p, that of war t_w. The rate of energy exchange during peace is an *increasing* function of time since the population increases. The rate of energy exchange during war is a *decreasing* function of time, since gradually the population decreases. The total change of energy during t_p is $f_p(t_p)$, the change during t_w is $f_w(t_w)$. The average exchange per unit time is

$$f_a = \frac{f_p(t_p) + f_w(t_w)}{t_p + t_w}. \tag{37}$$

Depending on the form of f_p and f_w, f_a may have a maximum for a set of values t_p, t_w. Those values determine the corresponding average duration of peace and of war, while $t_w/(t_p + t_w)$ determines the frequency of incidence of wars.

In passing to the considerations of individual organisms, an interesting possibility at once suggests itself in regard to general internal structure and ontogenetic development of the latter.

The different organs of an organism interact with each other, the interaction resulting in energy flow towards or away from the organ. Let us denote by M_o the total mass of the organism, by M_i the masses of different organs. We may consider as a first approximation the energy flow from organ k to organ i as given by

$$a_{ik} M_i M_k . \tag{38}$$

Moreover the interaction of the organ i with the whole organism may be put in the form

$$a_{i0} M_i M_0 . \tag{39}$$

The interaction of an organ with the external environment may be taken as

$$b_i M_i . \tag{40}$$

The growth of an organ results in an exchange of energy which in general will be of the form.

$$c(M_i) \frac{dM_i}{dt}. \tag{41}$$

We may now introduce a Hamiltonian principle for the organism, of the form

$$\int_{t_1}^{t_2} (\delta F + \Sigma Q_i \delta M_i) = 0$$

with

$$F = \sum_i \sum_k a_{ik} M_i M_k + \sum_i b_i M_i ;$$

$$Q_i = -\frac{1}{M_i} \frac{dM_i}{dt} ; \quad \Sigma M_i = M_0 .$$

This will give us a system of differential equations, determining the variation of different M_i's. As initial condition we may put all

M_i zero except M_0. This is the condition of an undifferentiated ovum. The gradual development of the different organs should then be described by the system of differential equations.

By a similar argument as in section *II*, we may limit our considerations to only a few more important organs, such as alimentary tract, circulating system, respiratory system, muscles, and nerves. The values of a_{ik}'s may then either be calculated from theoretical considerations, or determined by comparison of the integral curves of the system of differential equations with actual embryological observations.

The variational principle may be applied also to problems which have already been dealt with in mathematical biophysics. In the theory of the central nervous system we usually introduce hypothetical structures, consisting of excitatory and inhibitory fibers, and invent more or less those structures *ad hoc* to explain certain phenomena. We may however proceed now in a more satisfactory way. Developing first an abstract theory of neuronic network, along the lines initiated by A. S. Householder and Walter Pitts, we may then put the problem in this way: For a given sequence and type of stimuli, which of the theoretically possible structures will give rise to the greatest energy interchange? A structure adopted on this principle will be free from the *ad hoc* nature, inherent in structures studied hitherto. It may perhaps be generally proven, that any such structure will have to contain both excitatory and inhibitory fibers, and thus the introduction of the latter will cease to be an independent hypothesis.

If excitation results in energy release, then our concept of pleasure as a general excitatory phenomenon and pain as a general inhibitory phenomenon may be reformulated thus: any situation which increases the total positive energy flow within the organism is pleasant, any situation that decreases it is unpleasant.

Application of the extremum principle to individual cells may be illustrated on the problem of cell division.

Using H. D. Landahl's (1942) notations, we shall find in general that the energy flow, both *inside the cell, and between the cell and its surroundings,* is a function $F(\varepsilon, r, \frac{d\varepsilon}{dt}, \frac{dr}{dt})$ of ε, r, $d\varepsilon/dt$ and dr/dt. The quantity $d\varepsilon/dt = \dot{\varepsilon}$ enters into the function F in two different ways. First of all, during the process of elongation, as the surface of the cell increases, there is a transformation of some other form of energy into the additional surface energy. The rate of that transformation depends on $d\varepsilon/dt = \dot{\varepsilon}$. Second, the dissipation of energy due

to viscous friction depends on $\dot{\varepsilon}$. In a similar way $dr/dt = \dot{r}$ is introduced.

By requiring

$$\delta \int_{t_1}^{t_2} F \, dt = 0$$

we find the system of simultaneous differential equations

$$\begin{aligned} \frac{d}{dt}\left(\frac{\partial F}{\partial \dot{\varepsilon}}\right) &= \frac{\partial F}{\partial \varepsilon} \\ \frac{d}{dt}\left(\frac{\partial F}{\partial \dot{r}}\right) &= \frac{\partial F}{\partial r}. \end{aligned} \tag{42}$$

We thus describe the elongation and constriction by one set of equations, instead of treating them separately, as hitherto. This must be considered as a definite advantage.

The energy flows include such things as the dissipation of energy in the diffusion fields, as well as the energy transformations in various metabolic reactions. The calculation of the former will involve the diffusion coefficients, permeabilities, and reaction rates. The calculation of the latter will involve again the reaction rates and also the heats of reactions. Thus the cell division curves will depend also on the latter, as one naturally should expect. The missing of the heats of reactions, and of the general energetics of the cell, from the present theory of cell division has been one of its defects. The whole problem is treated in a separate paper.

As a last illustration we may apply our general principle to the problem of frequency distribution of words of different lengths. A spoken word results in certain activities, overt or covert, and thus speech produces energy transformation. Let the number of words of length l be N_l. The energy transformation produced by a word will be in general a function $f(l)$ of its length, that for purely physiological reasons. But the energy flow created by a spoken word will also depend on the frequency of use of that word in the speech, and be a function $U(N_l)$. In the collection of words of different lengths, the total energy flow will be

$$\sum_{l=0}^{l=\infty} N_l [f(l) + U(N_l)]. \tag{43}$$

The requirement of maximum of (43) gives

$$f(l) + U(N_l) + N_l \frac{dU}{dN_l} = 0. \tag{44}$$

If we assume as an example only

$$f(l) = a \log l\,, \qquad U(N_l) = b \log N_l\,, \tag{45}$$

which may be made plausible by psychological considerations, equation (44) gives

$$a \log l + b \log N_l + b = 0\,. \tag{46}$$

G. Zipff (1935, p. 23 ff.) has studied quantitatively the relations between the frequency of occurrence of words and their lengths, in different languages. Such data may be used to verify such or similar relations as the above.

The author is indebted to Dr. Alston S. Householder and to Dr. Herbert D. Landahl for reading the manuscript and valuable comments.

LITERATURE

Lotka, A. J. 1922a. "Contributions to the Energetics of Evolution." *Proc. Nat. Acad.*, 8, 146-151.

Lotka, A. J. 1922b. "Natural Selection as a Physical Principle." *Proc. Nat. Acad.*, 8, 151-154.

Rashevsky, N. 1941. "A Note on the Nature of Correlations Between Different Characteristics of Organisms." *Bull. Math. Biophysics*, 3, 93-95.

Rashevsky, N. 1942. "Contributions to the Mathematical Theory of Human Relations: V." *Psychometrika*, 7, 117-134.

Volterra, V. 1931. *Leçons sur la Theorie Mathematique de la lutte pour la vie.* Paris: Gauthiers-Villars.

Whittaker, E. T. 1927. *A Treatise on the Analytical Dynamics of Particles and Rigid Bodies.* The University Press: Cambridge.

Zipff, G. 1935. *The Psycho-Biology of Language.* Boston, Houghton Mifflin Co.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

NOTE ON THE HAMILTONIAN PRINCIPLE IN BIOLOGY AND IN PHYSICS

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

A suggestion is made to establish a general variational principle of which the recently discussed principle of maximum energy exchange in biology and the usual Hamiltonian principle in physics would be particular cases.

In a previous publication (Rashevsky, 1943), we have formulated mathematically a hypothesis stated some time ago by Alfred J. Lotka (1922 a, b), namely, that the course of events in the biological world is determined by maximizing the total energy exchange between different biological units. We have suggested that this principle may be stated in form of a variational principle. If x_i's are any kind of biological quantities that determine the energy exchanges in a biological system, and $\dot{x}_i$'s are the corresponding derivatives with respect to time, we construct a "Hamiltonian" $F(x_1, \cdots x_n, \dot{x}_1 \cdots \dot{x}_r)$, and require

$$\delta \int_{t_1}^{t_2} F\, dt = 0, \tag{1}$$

so as to maximize the integral. Numerous possible applications of that principle to a great variety of biological problems have been discussed in *loc. cit.*

In physics, the "Hamiltonian" H is a function of the generalized coordinates q and momenta p, and we have

$$\delta \int_{t_1}^{t_2} H\, dt = 0, \tag{2}$$

minimizing the integral.

The question naturally arises as to whether principle (1) may not be reduced to (2), so as to avoid a duality of living and non-living. This does not seem likely, and A. J. Lotka (1922 a, b) has proposed his hypothesis as an independent principle. It must be remarked that F has the dimension of energy flow, hence $[F] = ml^2\, t^{-3}$, while H has the dimension of energy, and therefore $[H] = ml^2\, t^{-2}$. One might per-

haps think that in some way both principles operate simultaneously, both in the living and non-living, but that the role of the first principle is more pronounced in the living world, that of the second in the non-living. The most natural suggestion would be to put

$$\delta \int_{t_1}^{t_2} (\alpha_1 F - \alpha_2 H)\, dt = 0, \tag{3}$$

and assume that the first term prevails in the living, the second in the non-living. If, however, we make such an assumption, we must assume α_1 and α_2 to be of different physical dimensionality, so as to make $\alpha_1 F$ and $\alpha_2 H$ of the same dimensionality. This introduces a rather unpleasant indefiniteness.

It may be suggested that α_1 and α_2 be chosen so as to make the whole integral in (3) a pure number. This would give

$$[\alpha_1] = m^{-1} l^{-2} t^2; \quad [\alpha_2] = m^{-1} l^{-2} t. \tag{4}$$

We may make the hypothesis that α_1 and α_2 are two universal constants. All systems for which $\alpha_1 F >> \alpha_2 H$ we may define as biological; all systems for which $\alpha_1 F << \alpha_2 H$ we may define as physical. For each of those classes both α_1 and α_2 drop out of the picture. But when $\alpha_1 F$ is comparable to $\alpha_2 H$, we have intermediate systems in which α_1 and α_2 play a role.

However, inasmuch as mathematically only the ratio $\tau = \alpha_1/\alpha_2$ is important in the variational problem given by equation (3), therefore it may be better to leave the integral of the dimension energy $\times$ time by putting

$$\delta \int_{t_1}^{t_2} (\tau F - H)\, dt = 0. \tag{5}$$

We may assume τ, which has the dimension of time, to be a universal constant characteristic of biological phenomena. If τ is very small, then systems in which energy exchanges are not too large fall into the domain of physics. Systems in which the energy exchanges play a preponderant role fall in the domain of biology. When τF is comparable to H we have borderline systems. Such may be perhaps the case of single cells. By developing a theory of such systems, we may determine the constant τ from any comparison of quantitative data with the theory.

If principle (5) is to hold quite generally, then it must also describe the process of the beginning of life from the non-living. Since in this process we must obviously have a borderline case, therefore we shall have to consider the general expression (5) in which τF and

H are comparable. In the latter stages of development of the organic world the H term will become negligible, and we shall have the restricted form given by equation (1). This restricted form should not, however, be able to account for the origin of life. This throws some light upon the difficulty which we encountered in this respect in *loc. cit.* (p. 54).

In actual applications to borderline cases, we find that friction forces play a prominent part. In this case, even in purely physical systems, the Hamiltonian principle cannot be applied in its form (2). Instead, denoting by $f_i(dx_i/dt)$ the frictional forces which are proportional to the values of dx_i/dt, we have (Whittaker, 1927, p. 249):

$$\int_{t_1}^{t_2} (\delta H + \sum_i f_i \frac{dx_i}{dt} \delta x_i)\, dt = 0. \tag{6}$$

If, as is practically always the case in systems that interest us here, the inertial terms are negligible, H depends only on the x_i's, and the principle (6) leads to equations of the form:

$$f_i \frac{dx_i}{dt} + \frac{\partial H}{\partial x_i} = 0, \tag{7}$$

which express the equality of the friction forces and those derived from potential H. An estimation of the terms of F, that depend on dx_i/dt indicate, as will be shown elsewhere, that they are in actual cases vanishingly small as compared with terms depending on x_i's. Hence the generalized Hamiltonian principle which covers both physical and biological phenomena will be of the form

$$\delta \int_{t_1}^{t_2} (\tau\, \delta F - \delta H - \sum_i f_i \frac{dx_i}{dt} \delta x_i)\, dt = 0. \tag{8}$$

That principle leads to the equations

$$f_i \frac{dx_i}{dt} + \frac{\partial H}{\partial x_i} - \tau \frac{\partial F}{\partial x_i} 0. \tag{9}$$

Equation (9) shows that in the general case, $\tau\, \partial F/dx_i$ plays formally the role of a force derived from a potential. If F is small, we have the equations (7) of physics. If F is large, we have, for purely biological systems, the equations

$$f_i \frac{dx_i}{dt} - \tau \frac{\partial F}{\partial x_i} = 0. \tag{10}$$

The intermediate cases are described by equations (9).

The sharp distinction between living and nonliving thus vanishes. At the same time, however, we neither claim to *reduce* biology to physics, nor the reverse.

LITERATURE

Lotka, Alfred J. 1922a. "Contributions to the Energetics of Evolution." *Proc. Nat. Acad.*, 8, 146-151.

Lotka, Alfred J. 1922b. "Natural Selection as a Physical Principle." *Proc. Nat. Acad.*, 8 151-154.

Rashevsky, N. 1943. "Outline of a New Mathematical Approach to General Biology: II." *Bull. Math. Biophysics*, 5, 49-64.

Whittaker, E. T. 1927. *A Treatise on the Analytical Dynamics of Particles and Rigid Bodies.* The University Press; Cambridge.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 5, 1943

ON THE FORM OF PLANTS AND ANIMALS

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

The expression for the form of organisms in terms of their biological functions, outlined in a previous paper, is carried out somewhat more in detail. Making definite assumptions about functions left arbitrary in the previous paper, expressions for different shapes of plants are derived. In continuation of the previous paper, the relation between the amount of nervous tissue and the form of an animal is discussed in more detail.

Plants. We have shown previously (Rashevsky, 1943; referred to as *loc. cit.*), how in principle the gross shape of a plant may be determined by the values of its total mass M, and average rate of metabolism q per unit mass. As a further illustration of the method, but without any claim as to immediate applicability of the results, we shall, using the same notations as in *loc cit.*, derive explicit expressions by making specific assumptions about the functions $f(r, \delta)$, $f_0(r_0, \delta, \mathrm{M})$ and $f_1(qM, \delta)$, which were left undetermined.

A very rough idea about f may be obtained in the following manner. A horizontal rigid rod of length l, fixed at one end and loaded at the other end with a load P, will sag at the free end by the amount (Geckeler, 1928)

$$x_0 = \frac{P}{3EJ} l^3, \tag{1}$$

where E is the modulus of elasticity and J is defined by

$$J = \int x^2 d\sigma . \tag{2}$$

Here x denotes the coordinate in the direction of the force P, and $d\sigma$ is the element of surface of the cross section. Hence the dimensionality of J is [cm^4]. From equation (1) we find the bending per unit length to be

$$\Delta x_0 = \frac{x_0}{l} = \frac{P}{3EJ} l^2, \tag{3}$$

and from the above dimensional considerations, this quantity will be, in general, of the form

$$\Delta x_0 \propto \frac{Pl^2}{3Er^4}. \tag{4}$$

On the other hand, considering that the rod bends under the influence of its own weight, we have

$$P \propto lr_0^2 . \tag{5}$$

Hence

$$\Delta x_0 \propto \frac{l^3\delta}{3Er^2}.$$

E is likely to increase with δ, and therefore, as a first approximation, we may put, assuming $E \propto \delta$:

$$\Delta x_0 \propto \frac{l^3}{r^2}. \tag{6}$$

When Δx_0 exceeds a certain constant determined by the strength of the wood, the branch breaks. That constant, in general, increases with δ. Let us put it proportional to δ^p. Then we have

$$l = a\,\delta^p\, r^{2/3}, \tag{7}$$

a being a coefficient. This determines f.

As regards f_0, we may consider that the trunk is compressed by a force $M/\pi\, r_0^2$ per cm^2 of cross section, and if that quantity exceeds a limit, which we again set approximately proportional to δ^p, the wood breaks under compression. Hence, b being another coefficient,

$$M = b\,\delta^p\, r_0^2. \tag{8}$$

The function f_1 may be determined roughly by considering that the total metabolic flow in the trunk, which is proportional to qM, is proportional to the cross section, and approximately inversely proportional to δ. Hence, with c as a coefficient,

$$qM = \frac{cr_0^2}{\delta}; \quad \frac{qM}{n} = \frac{cr^2}{\delta}. \tag{9}$$

Together with

$$M = \delta\,(l_0 r_0^2 + nlr^2) \tag{10}$$

and [*loc. cit.*, equation (27)]

$$qM = knlr\,, \tag{11}$$

equations (7), (8), and (9) determine δ, l_0, r_0, l, r, and n in terms of q and M.

Solving those equations, we find

$$\delta = \left(\frac{c}{bq}\right)^{1/(p+1)}; \quad l_0 = b\left(\frac{c}{bq}\right)^{(p-1)/(p+1)} - \frac{a^3k^2}{b^2q^2}\left(\frac{c}{bq}\right)^{p/(p+1)};$$

$$r_0 = \frac{M^{\frac{1}{3}}\, q^{p/2(p+1)}}{b^{1/2(p+1)}\, c^{p/2(p+1)}}; \quad l = \frac{a^3k^3}{b^2q^2}\left(\frac{c}{bq}\right)^{p/(p+1)}; \tag{12}$$

$$r = \frac{a^3k^3}{b^3q^3}; \quad n = \frac{b^{(6p+5)/(p+1)}\, Mq^{(7p+6)/(p+1)}}{a^6\, k^6\, c^{p/(p+1)}}.$$

If $p > > 1$, then l_0, as a function of q, is negative below a certain value q_1 of q, then becomes positive, reaches a maximum, and, remaining positive, decreases to zero, for $q = \infty$. A negative l_0, physically, would probably mean $l_0 = 0$, that is, a form of a bush. If the actual range of variation of q is in the neighborhood of q_1, then l_0 increases with q rather rapidly. For $p << 1$, l_0 is first negative, then increases to $+\infty$. Here again l_0 increases very rapidly with q in the neighborhood of q_1, though for large q, approximately $l_0 \propto q$. Assuming that the actual range of variation of q is in the neighborhood of q_1, we find that the ratio l_0/r_0 increases very rapidly with q. If $u(q)$ denotes a rapidly increasing function of q, then,

$$\frac{l_0}{r_0} \propto \frac{u(q)}{\sqrt{M}}, \tag{13}$$

$$\frac{l}{l_0} \propto \frac{1}{q^2 u(q)}, \tag{14}$$

$$n \propto Mq^{\mu}, \ (6 < \mu < 7). \tag{15}$$

$$\frac{r}{r_0} \propto \frac{1}{q^{\mu/2}\sqrt{M}}. \tag{16}$$

For a constant M, small q gives us a small l_0/r_0, large l/l_0, large r/r_0, and small n, hence a shape like in Figure 1a. An increasing q increases

a b c

FIGURE 1

l_0/r_0, and n, but decreases l/l_0 and r/r_0. We have the shape of Figure 1b. An increase of M increases n, and to a lesser extent decreases l_0/r_0 and r/r_0. Hence a large M, and sufficiently large q give us the shape of Figure 1c. The density δ decreases with increasing q, but if $p >> 1$, the variation is small.

All the above serves, of course, only as an illustration. It indicates clearly, however, that a theory may be developed on that basis, by considering more exact expressions for the different functions involved. It is important, however, that the expressions (12)-(16) are in principle verifiable experimentally and suggest definite new experimental problems.

Animals. In *loc. cit.* we have discussed some possible relations between the shape of an animal and the size of its central nervous system.

We shall conclude this paper by a few remarks in regard to the quantitative relations between the values n_1, n_2, n_4, and n_6, introduced in *loc. cit.*

The quantity n is measured approximately by the amount of nervous tissue necessary to produce and control movements of a given complexity. We may approximately put n proportional to the number of mechanical degrees of freedom of the lever-propelled metabolizing system. Denoting that number by m, we shall have, with A as a coefficient

$$n = Am . \tag{17}$$

But A itself will depend on at least two factors: one—the muscular tonus t_0 to be maintained in each muscle operating on one degree of freedom, and two—the amount of special coordination S needed to maintain postures which are mechanically unstable. Thus, with B as another coefficient

$$n = B(t_0 + S)m . \tag{18}$$

For simplicity, let us put $t_0 = \text{const}$. For a simple lever system represented in Figure 1a of *loc. cit.*, $m = m_1$ is very small and $S = 0$. Hence a small $n = n_1$. For a quadruped $m = m_4$ is larger, but $S = S_4$ is still rather small. Hence $n_4 = B(t_0 + S_4)m_4$ is larger than n_1. For a biped, m_2 lies between m_1 and m_4, but $S = S_2$ is very large, and therefore $n_2 = B(t_0 + S_2)m_2 > n_4$.

The quantity m can be calculated in principle relatively simply. The calculation of S presents greater difficulties. We may have to define properly the degree of mechanical instability of a system, and then set S approximately proportional to that quantity.

We may now state some of the previous conditions more precisely. For instance:

If $v < q/c$, and $n \geqslant B\ t_0\ m_1$, then we have an organism without extremities, propelling itself by crawling.

The case $v < q/c$, $n < B\ t_0\ m_1$ should not occur in nature.

If $v > q/c$, $n \geqslant B(t_0 + S_4)\, m_4$, we have a quadruped, the length of whose legs are determined by equations given in *loc. cit.*

If $v > q/c$, $n \geqslant B(t_0 + S_2)\, m_2$ we have a biped.

All the above statements are quantitative and can be checked experimentally.

The author is indebted to Dr. H. D. Landahl for reading the paper and for valuable criticism.

LITERATURE

Geckeler, J. W. 1928. "Elastostatik." *Handbuch der Physik*, 6, 165. Leipzig: J. Springer.

Rashevsky, N. 1943. "Outline of a New Mathematical Approach to General Biology: I." *Bull. Math. Biophysics*, 5, 33-47.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 5, 1943

A MECHANISM OF DIVISION OF A CELL WITH AN IMPERMEABLE MEMBRANE

H. D. LANDAHL
THE UNIVERSITY OF CHICAGO

The case of a cell in which metabolites are produced and consumed within the cell, without leaving the cell, is considered. Conditions are given under which there may be an excess production at the center over that at the periphery, and this condition is stable with respect to displacement of the center. The resulting diffusion forces are considered, and an expression is developed for the rate of elongation with time. The expression is very similar to that obtained by considering the flow of metabolites into and out of the cell.

In previous studies, a theory of cell division has been developed on the assumption that there is a net outward dividing force as a result of the interchange of metabolites between the cell and its surroundings (Rashevsky, 1940a; Landahl, 1942). In some cells there is very little interchange, while in others division takes place even though the various metabolic processes are markedly slowed down (Brachet, 1934). Thus it seems desirable to see if one can modify the theoretical mechanism so as to make it essentially independent of the interchange of materials with the surrounding medium.

We shall keep the mechanism as simple as possible and consider the effect of a single substance being produced at a rate q gms cm^{-3} sec^{-1}. If we wish to consider quasi-stationary states, it is necessary that the substance be consumed in the cell, as we shall neglect the flow out of the cell. Further, in order to have any concentration gradients, the production or consumption rate must vary with position. Suppose that q is constant throughout the cell. This may be the breaking down of large molecules into many smaller ones. Then let the rate at which the substance resynthesizes or disappears be proportional to the number density of a particular catalytic particle, as in N. Rashevsky's polar cell (Rashevsky, 1940b). Let the particles be free to move so that their distribution will be given by a Boltzmann distribution. We shall neglect the effect of gradients of concentration of the large molecules on the distribution of the catalyst as well in connection with the dividing force. Actually, one might expect several substances to be produced and consumed within the cell that also show concentration

gradients of the type discussed here. Not all would have the same effect and the resultant would be a weighted average. If the concentration were higher in the center than at the periphery, the catalytic particles would be denser near the periphery, thus tending to maintain the difference. We shall consider this in greater detail.

Consider a cell which has an axis of symmetry, the z-axis. Let $2r_1$ be the length along the z-axis, and $2r_2$ the width along the x-axis perpendicular to the z-axis. We shall treat the problem by using the approximation method (Rashevsky, 1940). Divide the cell as in Figure 1, so that $V_1 = V_3$ where V_i is the volume of section i, and V is

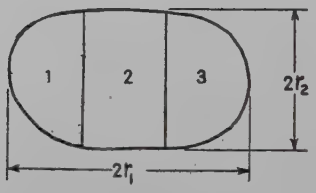

FIGURE 1

the volume of the cell. If c_i is the average concentration and n_i is the average number density of the catalyst in section i, we have

$$n_1 V_1 + n_2 V_2 + n_3 V_3 = nV, \tag{1}$$

and a similar expression for the c_i. In equation (1), n is defined by the equation as an average value of the number density of the catalyst for the cell as a whole.

If $\alpha RT/N$ is the constant of proportionality between the force on a catalytic particle and the negative of the concentration gradient, we have

$$n_i = n_j e^{-\alpha(c_i - c_j)} \tag{2}$$

to determine the distribution of the catalytic particles. R is the gas constant per mole, T is the absolute temperature, and N is Avogadros' number.

We next determine the conditions for the average concentration to be higher in section two than that in one and three. From the material balance conditions, we have, denoting by d_i the distance from the center of the cell to the center of section i,

$$\frac{dc_1}{dt} = q - an_1 - \frac{A\,D}{d_1\,V_1}(c_1 - c_2)\,, \tag{3}$$

$$\frac{dc_2}{dt} = q - an_2 - \frac{A\,D}{d_1\,V_2}(c_2 - c_1) - \frac{A\,D}{d_3\,V_2}(c_2 - c_3)\,, \tag{4}$$

and an expression for section three equivalent to (3) with subscript 1 replaced by subscript 3. A is the area of the plane separating section two from three or one. The constant a determines the rate of removal of the substance by the catalyst. First we shall let $d_1 = d_3$, that is, assume that the concentrations are symmetric with respect to the z-axis, thus $c_1 = c_3$, and similarly $n_1 = n_3$. Introducing equations (1) and (2) in (4), we have

$$\frac{dc_2}{dt} = q - \frac{2AD}{d_1\,V_2}(c_2 - c_1) - \frac{a\,n\,V}{2V_1\,e^{\alpha(c_2 - c_1)} + V_2}. \tag{5}$$

If $dc_2/dt = 0$, and $(c_2 - c_1) = 0$, equation (5) is satisfied, since $q = an$ from the definition of n in equation (1). We wish to know under what conditions $dc_2/dt > 0$, for $c_2 - c_1 > 0$, $c_2 - c_1$ being small. This condition is readily seen to be

$$\alpha\,V_1\,V_2\,d_1\,q > A\,V\,D\,, \tag{6}$$

that is, the force on the particle per unit gradient of concentration, or the production rate q, or the size of the cell must be large enough, or the internal diffusion coefficient D must be small enough, in order that a small increase in c_2 will cause a further increase. Similarly, we find that a small decrease in c_2 will cause a further decrease if inequality (6) holds. Thus (6) is the condition for the equilibrium $c_1 = c_2 = c_3$ to be unstable.

If $\alpha(c_2 - c_1)$ is sufficiently large, so that we may neglect the term containing $e^{\alpha(c_2 - c_1)}$ in the denominator, we may solve for $(c_2 - c_1)$ in equation (5) for the equilibrium value by setting $dc_2/dt = 0$, obtaining, for $c_2 - c_1 > 0$,

$$c_2 - c_1 = \frac{V_2\,d_1\,q}{2\,A\,D}. \tag{7}$$

If $V_1 \approx \frac{1}{2}V_2 \approx \frac{1}{4}\,V$, this is $\alpha(c_2 - c_1) = 2\alpha V_1 V_2 d_1 q/A\,D\,V > 2$ from (6). Then also, (7) may be made exact if the right side is multiplied by $\tanh \frac{1}{2}\,\alpha(c_2 - c_1) > .76$. If the left member of (6) exceeds the right by a factor of four, the correction factor differs from unity by but a few per cent.

Suppose next that the point of maximum in section 2 of Figure 1 is displaced slightly to the right, so that we may treat this effect approximately by introducing $d_1 > d_3$. We then wish to know whether the average concentration in section 3 will tend to rise or fall. If it rises, the maximum would tend to move to the right, and if this continued, we would have a polar cell (Rashevsky, 1940b). On the other hand, if c_3 falls, the maximum would be shifted back and the symmetric configuration can be considered stable.

From (3) and (2), we have for the stationary state

$$q - an_1 - \frac{A\,D}{d_1\,V_1\,\alpha}\log\frac{n_2}{n_1} = 0, \tag{8}$$

and a similar expression for section 3. Subtracting (8) from the corresponding equation with subscripts 1 replaced by 3, introducing $\delta = (d_1 - d_3)/d_1 < < 1$, and expanding $\log n_1/n_3$ for $n_1 - n_3 < < n_3$, we have on solving for $n_3 - n_1$,

$$n_3 - n_1 = \frac{A\,D\,\delta\,n_3 \log n_3/n_2}{an_3\,\alpha\,d_1\,V_1 - A\,D}. \tag{9}$$

Since we are taking $\delta > 0$, $c_2 > c_3$, thus $n_3 > n_2$, and $\alpha\,V_1V_2d_1q > A\,D\,V$ from (6), then $n_3 > n_1$, as $an_3 > q$, $V > V_2$. But $n_3 > n_1$ implies that $c_3 < c_1$ or c_3 falls below c_1, thus below its original value for $\delta = 0$. Thus the central maximum is a stable equilibrium if (6) holds.

Heretofore we have considered the stability with respect to the z-axis. In this case we found $(c_2 - c_1)_z$ to be given by equation (7). In a similar manner we could treat the stability with respect to x and obtain $(c_2 - c_1)_x$. However, in this case c_{2x} would not necessarily be the same as c_{2z}, whereas physically this must be so.

If we divide the cell, as in Figure 2, into a cylindrical central region 2, of volume V_2, a region 1 of volume V_1 surrounding region

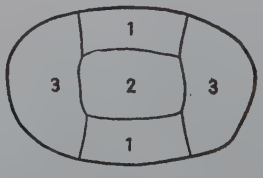

FIGURE 2

2 coaxially, and two regions comprising the "ends" of the cell and of volume V_3 together, we may write an equation formally the same as equation (1), and two independent equations of the form (2). We assume a center of symmetry. From these we may solve for n_i in terms of ξ and ζ where

$$\xi = \alpha(c_2 - c_1), \quad \zeta = \alpha(c_2 - c_3). \tag{10}$$

The c_i's are concentrations corresponding to the new divisions. For simplicity, set $V_1 = V_2 = V_3 = V/3$. We may also write three equations similar to (3) and (4). Note that $A_1 \neq A_3$ and $q = an$. Subtracting the first of these equations from the second, then the third from the second we have

$$\frac{d\xi}{dt} = 3\alpha q(e^{\xi} - 1)/(1 + e^{\xi} + e^{\zeta}) - 2K_1\xi - K_3\zeta, \tag{11}$$

$$\frac{d\zeta}{dt} = 3\alpha q(e^{\zeta} - 1)/(1 + e^{\xi} + e^{\zeta}) - K_1\xi - 2K_3\zeta, \tag{12}$$

where

$$K_i = 3A_iD/d_iV. \tag{13}$$

As $K_1 \sim K_3$, and if $\alpha q dV > 3KdV = 9AD$, which is essentially the same as (6), then $d\xi/dt > 0$ and $d\zeta/dt > 0$ if $\xi \sim \zeta$ are small positive values. Thus ξ and ζ continue to increase. If K_1 is nearly equal to K_3, and K is a value between K_1 and K_3, then for $e^{\xi} > > 1$, $\xi \doteq \zeta \doteq \alpha q/2K$, is a solution for the stationary state. Now let $\Theta = \zeta - \xi < < \xi$. We shall obtain a first approximation to Θ, expanding e^{Θ} and retaining the first degree terms. Letting $d\xi/dt = d\zeta/dt = 0$, and eliminating ζ by $\zeta = \xi + \Theta$, we have approximately

$$\Theta = \frac{(K_1 - K_3)\xi}{(K_1 - K_3)\xi + 3\alpha q - 2K_3}. \tag{14}$$

Introducing $\xi \doteq \alpha q/2K$, $\alpha q > > 2K/3$, and $6K > > K_1 - K_3$, equation (14) becomes

$$\Theta = \frac{K_1 - K_3}{6K}. \tag{15}$$

We consider next the influence of the concentration gradients on the shape of the cell and follow the approximation treatment developed by N. Rashevsky (1940a, Ch. iii). We assume that there are structures within the cell upon which the diffusion forces may act whose relative volume is μ, and that the force per unit volume is given by

$$F = -\frac{3}{2}\frac{RT\mu}{M}\,\text{grad}\,c. \tag{16}$$

The relative elongation rate $(dr_1/dt)/r_1$, $2r_1$ being the "length", is given by integrating over the surface and volume forces. The first is represented by the surface tension γ and contributes an amount (Rashevsky, 1940a, Ch. iii, eq. 24)

$$-\gamma(r_1 - r_2)/2r_1 r_2 \eta \tag{17}$$

where $2r_2$ is the width of the cell and η is its viscosity. The contribution from the volume forces is (cf. Rashevsky, 1940a, Ch. iii, eq. 9)

$$-3RT\mu(c_3 - c_1)/2M\eta, \tag{18}$$

where a factor of two is introduced here, because c_3 and c_1 are taken half way out from the center of the cell instead of at the "ends".

Adding the expressions (17) and (18), introducing (15), (13) and $(c_3 - c_1) = -\Theta/\alpha$, with $A = \pi r_0^2$, $d = r_0/2$, $A_1 = \pi r_1 r_2$, $A_3 = \pi r_2^2$, $d_1 = r_2/2$, $d_3 = r_1/2$, and setting

$$\varepsilon = (r_1 - r_0)/r_0, \tag{19}$$

we have

$$\frac{d\varepsilon}{dt} = A\varepsilon - B\varepsilon^2 - C\varepsilon^3 \cdots \tag{20}$$

with

$$A = \frac{1}{r_0}(K' - \frac{3\gamma}{4\eta}), \tag{21}$$

$$B = \frac{1}{4r_0}\cdot\frac{3\gamma}{4\eta}, \tag{22}$$

$$C = \frac{1}{24r_0}(-8K' + \frac{3\gamma}{4\eta}), \tag{23}$$

$$K' = \frac{3RT\mu r_0}{4M\eta\alpha}. \tag{24}$$

If we set $\alpha = \frac{3}{2}RTV_p/M$, so that the force on each catalytic particle of volume V_p is given by equation (1) of N. Rashevsky (1940a, Ch. iii), we have

$$K' = \frac{RT\mu r_0}{2\eta V_p N}. \tag{25}$$

Note that K' is independent of q. If one assumes that e^{Θ} is large compared to one, K' becomes proportional to q, but the above may not hold.

Equations (20) to (23) are very similar to the equations resulting from the case of an outflowing metabolite (Landahl, 1942, eq. 6—9). The derived parameter K' and γ/η are of the same order of magnitude as in the previous case. Note that $C < 0$, so that the slope curve (Landahl, 1942, Fig. 1) would have its maximum displaced slightly to the left of the middle, whereas the measured values have a maximum just to the right.

If we take $K' = 7 \times 10^{-4}$ (Landahl, 1942), $\mu = 10^{-1}$, and $\eta = \frac{1}{2}$, we obtain for the radius of the catalytic particles, $r_p = 1.6 \times 10^{-5}$ cm. Then, if $M = 10^2$, $\alpha = 2 \times 10^7$, so that the inequality (6) becomes

$$D < 20q . \tag{26}$$

The rate of accumulation of lactic acid in developing *Arbacia* eggs is of the order of 3×10^{-8} gm cm^{-3} sec^{-1}, (Hutchens et al, 1942) and the corresponding q must be at least as large. Thus if we consider lactic acid as being formed from large glycogen molecules, but also being resynthesized by the action of a catalyst, we have a special case of the mechanism assumed initially. Taking q to be somewhat greater than the rate of accumulation, $q \sim 10^{-7}$, then the diffusion coefficient for lactic acid within the cell should be of the order of 2×10^{-6}. But the value of the diffusion coefficient in water is 1.4×10^{-5} cm^2 sec^{-1}. Thus the ratio of the diffusion coefficient inside the cell to that outside must be less than one-seventh, or a correspondingly larger fraction if q is larger. But since these molecules are polar, the diffusion coefficient within the cell would be expected to be very much smaller than that in water, so that the ratio would be much less than one-seventh. Thus inequality (6) is satisfied for this special case.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

LITERATURE

Brachet, J. 1934. "Metabloisme de l'oeuf." *Arch. de Biol.*, 45, 611-727.

Hutchens, John O., Keltch, A. K., Krahl, M. E., and G. H. A. Clowes. 1942. "Studies on Cell Metabolism and Cell Division: VI." *Journ. General Psysiol.*, 25, 717-731.

Landahl, H. D. 1942. "A Mathematical Analysis of Elongation and Constriction in Cell Division." *Bull. Math. Biophysics*, 4, 45-62.

Rashevsky, N. 1940a. "*Advances and Application of Mathematical Biology.*" Chicago: The University of Chicago Press.

Rashevsky, N. 1940b. "Mathematical Biophysics of Biological Self-Regulation of Cell Polarity." *Bull. Math. Biophysics*, 2, 15-25.

SCOPE OF THE BULLETIN

1. The Bulletin is devoted to publications of research in Mathematical Biophysics, as contributing to the physicomathematical foundations of biology in their most general scope.

2. Papers published in the Bulletin cover physicomathematical theories as well as any other mathematical treatments of biological phenomena, with the exception of purely statistical studies.

3. Mathematical studies in physics or in borderline fields in which a direct connection with biological problems is pointed out are also accepted.

4. Emphasis is put upon the mathematical developments, but a description and discussion of experimental work falls also within the scope of the Bulletin provided that description or discussion is made in close connection with mathematical developments *contained in the same paper.*

5. Outside of the scope of the journal are papers of purely statistical nature or papers concerned only with empirical equations.

PREPARATION OF MANUSCRIPTS

All manuscripts should be typewritten double space. Equations should be numbered on the right consecutively. *Do not* use such notations as "equation 2a" or, "equation 5′ " etc. References should be all given at the end of the paper, arranged in alphabetic order by authors and for each author chronologically, following *exactly* the style used in the Bulletin. In text, reference should be made by giving in parentheses the name of the author followed by the year of publication. In case of several publications by the same author in the same year, use notations "1940a", "1940b", etc.

In writing equations, slanted lines should be used wherever possible.

Every paper is to be preceded by a short abstract.

Drawings should be prepared in a professional manner on white paper or tracing cloth following as closely as possible the style used in the Bulletin. They should be drawn approximately twice the scale of the finished reproduction. Lettering should be made by means of a lettering guide. If desired by the authors, drawings may be made at the Editorial Office according to author's instructions, at cost.